Request for Entry of Amendment filed November 19, 2002

Applicants file the present Request for Continued Examination in order to request entry of the amendment to claim 19 filed November 19, 2002.

Rejection of Claims 18 and 35-37 under 35 U.S.C. § 102(e)

In the Advisory Action mailed January 13, 2003, the Office maintains the anticipation rejection of claims 18 and 35-37 over Hanada et al. ("Hanada"; U.S. Patent No. 5,945,103). Applicants continue to traverse this rejection, and provide the following additional remarks.

Applicants first note that a *prima facie* case of anticipation is only established if the reference expressly or inherently teaches every element or limitation of the claim, including any functional limitations. M.P.E.P. § 2131. Claim 18 includes two ingredients: "thrombin" and a "noncovalently binding inhibitor of thrombin activity," and also contains a functional limitation that must be considered: "wherein the thrombin preparation is suitable for therapeutic purposes." The purpose of the functional language is to limit the scope of this claim to preparations that are physiologically tolerable and may, for example, be directly administered to a patient. Thus, for a thrombin preparation to anticipate Applicants' claim 18, it must contain the noncovalent inhibitor, and be in a physiologically tolerable form for therapeutic use.

To support this rejection, the Office commented that "it is clear in Hanada at col. 1, lines 6-18, that thrombin is well known for therapeutic purposes." (Advisory Action at

Hanada that the Office cited to reject Applicants' claims. (Office Action of November 23,

2001, at pages 5-6.) Applicants agree that thrombin in general is a useful therapeutic agent, but one cannot use any thrombin-containing preparation therapeutically. Therapeutically suitable preparations must be physiologically tolerable to a patient and must be biologically active. For example, unsterilized preparations, or preparations containing potentially harmful chemical agents are not physiologically tolerable and would be excluded from Applicants' claims.

Applicants have previously provided evidence that the intermediate solution of Hanada upon which the Office bases this rejection is not physiologically tolerable. (Office Action of November 23, 2001, at pages 5-6; Amendment of November 19, 2002, and exhibits therein.) Therefore, it does not fall within Applicants' claims. Instead, it comprises trialkylphosphates, which are added to kill viruses. (Hanada at col. 4, lines 13-37.) Trialkylphosphates are organic solvents used to disrupt biological membranes. (See Amendment filed November 19, 2002, and exhibits therein.) Thus, they have the potential to kill not only viruses, but also human cells. Indeed, these compounds are skin irritants. (*Id.*) Further, Hanada teaches that these organic chemicals, as well as the thrombin inhibitors, should be removed before preparing the final pure thrombin solution. (Hanada at col. 5, lines 26-50.) Thus, Hanada itself implies that this intermediate solution is not a therapeutically suitable preparation.

Moreover, Applicants submit that the Office has failed to establish a *prima facie* case of anticipation in accordance with the substantial evidence standard of *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Instead, the Office has merely stated that "[t]he

20, 2002, at page 3.) Such conclusory statements are not sufficient to support a *prima*

facie case, particularly when Applicants have submitted evidence and scientific reasoning supporting a conclusion that the solutions are not the same. *See In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

The Office bears the burden to present evidence or factually supported reasoning explaining why the Hanada intermediate comprises all of the elements of claim 18 as well as those of claims 35-37, including the functional element of therapeutic suitability and the requirement of claim 37 that "after 12 months of storage at 20-25 °C, the thrombin maintains at least 70% of its original level of activity." Without such evidence, the present rejection is not a *prima facie* case of anticipation.

Applicants also note that the Hanada solution could, *arguendo*, only anticipate Applicants' claims under the high standard of inherency, because Hanada does not teach that the trialkylphosphate-containing intermediate is therapeutically tolerable. Thus, the Office must establish that the Hanada intermediate necessarily functions in accordance with or includes all of the limitations of claims 18 and 35-37. As the Federal Circuit has explained, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-9, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991.) To support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the Hanada solution, despite the presence of the trialkylphosphates, is necessarily therapeutically suitable. *See In re Oelrich*, 666 F.2d

1464 (Bd. Pat. App. & Int. 1990); *see also* M.P.E.P. § 2131.01 (III). Because the Office

has not provided any such showing, it has not established a *prima facie* case of anticipation, and Applicants request the withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

The Office also rejects claim 38 over Hanada under 35 U.S.C. § 102(e) or alternatively under § 103(a), and rejects claims 18, 19, and 35-38 under § 103(a) over Hanada in combination with Brezniak et al. ("Brezniak"; *Blood Coagulation and Fibrinolysis*, 5: 847-8 (1994)) and Altshuler et al. ("Altshuler"; U.S. Patent No. 4,363,319). (See Amendment filed November 19, 2002, at pages 6-8.)

Applicants traverse these rejections for the same reasons, given above, that Applicants traverse the § 102(e) rejection of claims 18 and 35-37. Hanada does not teach the subject matter of claims 18 and 35-37 because the solution in Hanada that contains a "noncovalently binding inhibitor of thrombin activity" is not a therapeutically suitable solution. (Hanada at col. 4, lines 13-37.) At the same time, the final solution in Hanada does not contain any thrombin inhibitor. Instead, it is a pure thrombin solution. (Hanada at col. 5, lines 25-50.)

In order for a combination of references to render a claim obvious, there must be both a suggestion or motivation to modify the references or to combine their teachings and a reasonable expectation of success in performing the combination. M.P.E.P. § 2142. Moreover, the motivation to combine the references and the reasonable expectation of success must both be found in the references themselves or in the

mere fact that the references can be combined or modified does not itself render the

combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Instead, the modification or combination must be desirable. *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000).

Applicants submit that there is no motivation in Hanada alone, or in combination with Brezniak and Altshuler, to add a noncovalently binding inhibitor of thrombin activity to a therapeutically suitable thrombin solution. Hanada itself does not suggest adding an inhibitor of thrombin activity to that therapeutic solution, but only teaches adding it as part of trialkylphosphate treatment and removing the components of the trialkylphosphate treatment before preparing a pure thrombin solution. (Hanada at col. 4, lines 13-37, and col. 5, lines 25-50.) Thus, Hanada, in fact, teaches away from adding such an inhibitor to a therapeutic thrombin solution. Neither Brezniak or Altshuler address this issue.

Moreover, the Office's reliance on Hanada is supported only by its assertion that Hanada teaches a composition that is "the same" as that of claim 18. (Office Action of June 20, 2002, at page 3.) Applicants note that the substantial evidence standard of *In re Zurko* and *In re Lee*, however, also applies to rejections under § 103(a). Thus, the Office "cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies." *In re Lee*, 61 U.S.P.Q.2d at 1435.

The Office has provided no factually supported rationale or evidence supporting its assertion that Hanada anticipates Applicants' claims. However, Applicants have

of claim 18. The Office bears the burden to support this rejection with evidence or

factually supported scientific reasoning. Because the Office has failed to do so, it has not established a *prima facie* case of obviousness. For these reasons, Applicants claims are unobvious, and Applicants request that this rejection be withdrawn.

Please grant any extensions of time required to enter this response and charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: February 19, 2003

By: _____
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